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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/942,098	08/28/2001	Lance E. Steward	17451 (BOT)	6185

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,098	STEWARD ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,45-53,57-67 and 96-148* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8,45-53,57-67 and 96-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed March 1, 2005 is acknowledged and has been entered. Claims 1-3, 9-44, 54, 56 and 68-95 have been canceled. Claims 4, 45-50, 52, 53, 55 and 57-60 have been amended. New claims 96-148 have been added. Claims 4-8, 45-53, 57-67 and 96-148 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or Applicants' comments with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 4-8, 45-53, 55, 57-67 and 96-148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (6762280), Holskin et al 1995 (Analytical Biochemistry, 226:148-155) taken with Mahajan et al (Chemistry and Biology, 1999, 6:401-409).

Schmidt et al teaches substrates for clostridial neurotoxins and that these substrates can be modified peptides or proteins that can serve as FRET substrates (abstract; col. 4). Schmidt et al teaches that Botulinum serotype A cleaves the protein SNAP-25 and that because botulinum neurotoxins are proteases, practical assays for this activity could form the basis for detection, quantification and drug-screening systems (col. 1). Schmidt et al teaches substrate peptides suitable for use in fluorescence resonant energy transfer assays (FRET), also known as

quenched-signal assays, for the protease activities of clostridial neurotoxins (col. 3). Schmidt et al teaches "FRET substrates for proteolytic activities of clostridial neurotoxins. Each contains a fluorescent group (fluorophore) on one side of the cleavage site, and a molecule that quenches that fluorescence on the other side of the cleavage site. Upon neurotoxin-catalyzed hydrolysis, the fluorophore and quencher diffuse away from each other, and the fluorescence signal increases in proportion to the extent of hydrolysis." (col. 5; see also col. 7). The amino acid sequences set forth in pending claims 7 and 8 are in Schmidt et al (see Schmidt et al SEQ ID NO: 11 and 12). Claims 59-67 define the number of amino acid residues that the peptide of the substrate should have, and these limitations are taught in Schmidt et al (see SEQ ID NO: 11 and 12). The human SNAP-25 sequence is taught in Schmidt et al. The claims also recite the defined sequence or a peptidomimetic thereof, which would be any variation of the BoNT/A taught or suggested in Schmidt et al.

Holskin et al teaches substrates that comprise a donor fluorophore, acceptor fluorophore and a protease having a specific cleavage site (abstract). Holskin et al teaches the specific fluorophores of EDANS and DABCYL (abstract). Holskin et al teaches that donor and acceptor pair EDANS and DABCYL, respectively, have excellent spectral overlap properties resulting in efficient energy transfer and that strategies incorporating this donor/acceptor pair have been successfully applied to fluorescence-based assays for HIV protease, renin as well as others (p. 149, col. 1; p. 152).

Mahajan et al teaches, as stated in the specification (p. 86), donor fluorophore or acceptor can be a genetically encoded dye such as green fluorescence protein (GFP), blue fluorescence protein (BFP), cyan fluorescence

protein (CFP), yellow fluorescence protein (YFP) or red fluorescence protein. Such genetically encoded donor fluorophores and acceptors are well known in the art as described in Mahajan et al. The prior art teaches that this type of technology (labeling substrates, proteins or DNA with fluorescence for use in assays) with can be used in screening of reagents or for diagnostic purposes.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Schmidt et al with Holskin et al to prepare a substrate complex as taught in Schmidt et al and Holskin et al, a fluorescence-based assay, which has the donor and acceptor fluorophores and the substrate with the substrate being a clostridial toxin. Although Holskin et al does not specifically teach BoNT/A the prior art does teach this concept with several other proteins and substrates to assay for potency of therapeutic compositions and to monitor potential inhibitors. Therefore, the use of SNAP-25 and BoNT/A in a similar substrate complex would have been obvious to a person of ordinary skill in the art with the reasonable expectation of success since it had been proven successful in other substrate compositions; especially in view of the fact that Schmidt et al teaches the use of FRET assays to monitor for therapeutic compositions or potential inhibitors. Mahajan et al teaches that the donor or acceptor fluorophores can be genetically encoded, and that this technique can be used to study enzyme activity or monitor for reagents in a high-throughput screening process. Therefore, modification of the donors or acceptors is within the skill of a person of ordinary skill in the art at the time the invention was made. With regard to the specifically claimed number of amino acids in the substrate, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the number of amino acids in the substrate in view

of the prior art teaching that the composition of the substrate can vary and since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). The claimed invention is prima facie obvious in view of the prior art teachings as a whole, absent any unexpected evidence to the contrary.

4. No claims are allowed.

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
June 13, 2005